Treatment of gonorrhoea with a single oral dose of minocycline

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The gradual decrease in susceptibility of the gonococcus to penicillin has led authorities to recommend ever larger doses for the therapy of gonorrhoea. The current recommendation of the U.S. Public Health Service for the treatment of infections in women is the administration of 4.8 m.u. aqueous procaine penicillin; one half that amount is advised for cases in men.

In seeking alternative antibiotics for the treatment of gonorrhoea, we have recently completed a trial of minocycline (7 dimethylamino-6-deoxy-6-dimethyltetracycline), a new semisynthetic derivative of tetracycline. The preparation and some biological properties of minocycline were described by Martell Subsequent investigations and Boothe (1967). (Fedorko, Katz, and Allnoch, 1968; Frisk and Tunevall, 1969; Washington, Yu, and Martin, 1970) have shown minocycline to have a broad spectrum much like tetracycline, with apparently more activity against the staphylococcus than tetracycline. Martin, Lester, Kellogg, and Thayer (1969) found that gonococcal strains isolated from patients after failure of treatment with penicillin were inhibited in vitro by minocycline at lower concentrations than was the case with tetracycline or doxycycline. The minimum inhibitory concentration (MIC) of minocycline ranged from 0.125 to 1.0 μg./ml. (mean 0.52); for tetracycline the MIC ranged from 0·125-2·0 μg./ml. (mean 0·75). Steigbigel, Reed, and Finland (1968a) tested 25 gonococcal strains in vitro and found minocycline to be more active than six other tetracyclines, 80 per cent. of the strains being inhibited by 0.4 µg./ml. or less. Steigbigel and others (1968b) also showed that single oral doses of 150 or 300 mg. minocycline gave higher and more prolonged serum levels than tetracycline. However, their subjects experienced significant nausea following the 300 mg. dose. Furthermore, their data show a mean serum level of minocycline

greater than $0.4~\mu g./ml.~24$ hours after both the 300 and the 150 mg. doses.

Because these studies indicated that minocycline might fit the need for an oral antigonococcal agent effective in the form of a single dose, a clinical trial was felt to be worth while.

Material

During an 8-month period, 170 men presenting at the Houston Social Hygiene Clinic for treatment of a urethral discharge were selected for the study. Criteria for acceptance of these males into the study included a Gramstained urethral smear showing typical intracellular Gram-negative diplococci and a positive culture for N. gonorrhoeae. Eleven non-pregnant females with genital secretions culturally positive for N. gonorrhoeae were also included in the study.

Method

Using sterile cotton-tipped applicator sticks, urethral or cervical exudate from each subject was cultured on Thayer-Martin selective medium. The cultures were incubated in a candle jar at 37°C. and examined at 24 hours. Identification of N. gonorrhoeae was confirmed by finding Gram-negative diplococci with typical colony characteristics giving a positive oxidase reaction.

Patients were treated with a single dose of minocycline and observed for 30 minutes for side-effects. The men were instructed to return within one week and the women within 2 weeks for follow-up examination and re-culture as is the routine in this clinic. On return each individual was questioned regarding sexual contact and the occurrence of any side-effects. Patients with a post-treatment positive culture result were considered to indicate therapeutic failure regardless of clinical findings. The majority of men returning did so within one week and those who did not return within 14 days were excluded from the study.

Estimations of the MICs of minocycline and tetracycline, as determined by the tube dilution method, were carried out by the Bio-Assay Laboratory, Dallas, Texas, on cultures of *N. gonorrhoeae* obtained from 107 of the male subjects.

Results

The results of treating 170 male patients are shown in the Table. Eleven received a single dose of 200 mg., 31 of 300 mg., and 128 of 400 mg. There were three cases of failure among the four patients who returned after receiving 200 mg. minocycline. Of the sixteen patients treated with 300 mg. who were available for follow-up, four showed failure. Of the 35 patients who returned after treatment with 400 mg., ten showed failure.

Of the eleven women who were treated with a single oral dose of 400 mg. of minocycline, seven returned for follow-up culture. All seven were clinically free of gonorrhoea and had negative results to cervical cultures when seen 11 and 16 days after treatment.

The MICs of minocycline and tetracyline were in the same general range with a median MIC of $0.5 \, \mu g./ml$. for each (Figure).

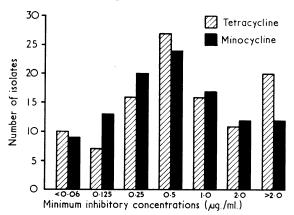


FIGURE Minimum inhibitory concentrations (µg./ml.) of tetracycline and minocycline in 107 isolates of N. gonorrhoeae

Only one patient reported any side-effects; in this case nausea and vomiting occurred 30 minutes after a 400 mg. dose and treatment was not successful. This patient was excluded from the series.

Discussion

Our failure rates were much higher than those reported by Thatcher, Pazin and Domescik (1970)

using minocycline in the treatment of gonococcal urethritis in men. Their failure rates in patients returning within 96 hours ranged from 8 per cent. after a 200 mg. dose to 4.5 per cent. after both 300 and 400 mg. doses. By contrast, in the present study, any of the three doses employed was clearly inadequate for the treatment of acute gonococcal urethritis in males. The most likely explanation for this is the insufficient duration of an adequate serum level after the single oral dose. The peak serum level is probably not the responsible factor, since increasing the dose from 300 to 400 mg. did not result in a higher cure rate in either this study or that of Thatcher and others (1970). Sensitivity studies were performed only in the present study and it is possible that our patients were infected with more resistant strains of N. gonorrhoeae. There was nevertheless no clear correlation between treatment failure and the less sensitive organisms. Certainly the strains isolated in our cases were not more sensitive to minocycline than to tetracycline as previous in vitro studies have indicated. A difficult problem in drug evaluation is the establishment of cure. A short follow-up period of only 48 to 96 hours may provide a falsely high cure rate because of suppression of signs of infection, whereas a longer follow-up of 1 to 2 weeks may be complicated by the inability to distinguish reliably between treatment failure and re-infection; this is true in all but confined groups of patients.

During 1967 in this clinic tetracycline hydrochloride (500 mg. 6-hourly for six doses) was administered to 118 men with gonococcal urethritis proven by culture; 52 returned and eleven (21 percent.) were classified as showing treatment fail re (unpublished data).

In a separate study carried out immediately after the conclusion of the minocycline study, tetracycline hydrochloride (2 g. initially followed after 4 hrs by 1 g.) was administered to 88 males with acute gonorrhoea proven by culture; 45 cases were re-examined within 1 week and six (13 per cent.) were classified as failures on the basis of positive cultures (unpublished data)

Thus, in our clinic population, it appears that 300 mg. minocycline administered in a single oral dose is equivalent in effect to 3 g. tetracycline HCl administered in six divided doses but less effective

TABLE Results in 170 patients

Single oral dose (mg.)	No. of patients treated	No. of defaulters	No. followed up	No. of failures	Percentage failure of those followed up
200	11	7	4	3	75
300	31	15	16	4	25
400	128	93	35	10	28.6

than 3 g. tetracycline given in two doses in the treatment of acute gonococcal urethritis in men. A single oral dose overcomes the uncertainties associated with multiple oral doses; the latter have been condemned for several reasons, but chiefly because it can never be known whether the patient has taken the medicine as prescribed.

Defaulters constitute a significant problem in evaluating the effectiveness of therapy in acute gonorrhoea. Some workers (Tiedemann, Hackney, Simpson, and Price, 1962; Lentz, MacVicar, and Beilstein, 1962) have demonstrated by administering placebos that approximately 90 per cent. of patients with treatment failure return within 2 weeks for retreatment. This, of course, can only apply to symptomatic males. In assessing drug trials at the Houston Social Hygiene Clinic, we always disregard the male and female defaulters; this weights the results toward a higher failure rate, but enables comparison with other studies.

In the study of Thatcher and others (1970) no side-effects occurred in 64 patients treated with 200 mg. minocycline, but fifteen of 110 and eleven of 22 who were followed up after treatment with 300 mg. and 400 mg. respectively experienced nausea. In the present study only one patient out of 55 who returned had experienced nausea and vomiting.

No conclusions regarding the treatment of uncomplicated gonorrhoea in cases in women can be drawn from the small number reported here, but the results are encouraging enough to warrant a larger study.

Summary

In the search for an antibiotic for the treatment of gonorrhoea effective in a single oral dose, minocycline, a new synthetic derivative of tetracycline, was administered in a dose of 200, 300, or 400 mg. to 170 men and eleven women with culturally proven acute gonorrhoea. After the 200 mg. dose of minocycline, urethral cultures in three out of four men returning for examination were positive. Both the 300 mg. and the 400 mg. doses yielded failure rates of approximately 25 per cent. in men. However, all

seven women who were followed up were clinically and culturally free of gonorrhoea after being treated with the 400 mg. dose. Although no conclusion can be drawn from such a small number of cases, the results were considered to justify a larger study of cases in women.

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Traitement de la gonococcie avec une dose orale unique de minocycline

SOMMAIRE

Dans l'idée de rechercher un antibiotique efficace en dose orale unique dans le traitement de la gonococcie, un nouveau dérivé synthétique de la tétracycline, le minocycline, fut prescrit aux doses de 200, 300, ou 400 mg. à 170 hommes et 11 femmes dont la gonococci aigüe avait été établie par culture. Après une dose de 200 mg. de minocycline, la culture urétrale redevint positive chez 3 des 4 hommes suivis. Aussi bien 300 mg. que 400 mg. entraîna un pourcentage d'échec d'environ 25 pour cent chez les hommes. Cependant, toutes les 7 femmes qui furent suivies après un traitement par 400 mg. furent cliniquement guéries et les cultures furent négatives. Bien qu'aucune conclusion ne puisse être dégagée d'un si petit nombre de cas, les résultats sont considérés comme justifiant une étude plus large chez la femme.